ORIGINAL ARTICLE

Familial aggregation and excess maternal transmission of type 2 diabetes in Tunisia

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Aim: To evaluate the degree of familial aggregation of type 2 diabetes mellitus in Tunisia and to investigate transmission patterns of the disease and their relationships with patients' clinical profiles.

Methods: Family history of diabetes and clinical data were collected for 132 unrelated type 2 diabetic Tunisian patients. Diabetes status was recorded for first degree relatives (parents, siblings) and second degree relatives (aunts and uncles from both maternal and paternal sides). Information about family history of diabetes was gathered for a total of 1767 individuals.

Results: Familial aggregation of type 2 diabetes was prominent and more important among first degree relatives than among second degree relatives ($p = 0.01$). Among studied subjects, 70% reported at least one relative with diabetes and 34% had at least one parent with diabetes. Diabetes was more frequent among mothers than fathers of probands ($p = 0.03$). This maternal effect extends to second degree relatives as diabetes was more common among maternal than paternal aunts and uncles ($p = 0.01$). There is no significant difference in clinical and metabolic profiles between patients according to transmission patterns of the disease.

Conclusion: These results suggest familial aggregation and excess maternal transmission of type 2 diabetes in the Tunisian studied population.

Type 2 diabetes mellitus (T2D) is a common metabolic disorder, characterised by hyperglycaemia caused by impaired glucose homeostasis, and represents a serious public health problem in many developed countries. The prevalence of T2D is increasing at the global level with large variation from one population to another depending on the ethnic origin.[1 2] In Tunisia, like in other developing countries, there is a growing concern for the important socioeconomic impact of the disease—high medical costs and altered quality of life.[3 4] T2D is a multifactorial syndrome depending on complex interactions between environmental and genetic factors. It has been widely reported that the occurrence of T2D is triggered by a genetic susceptibility, as indicated by monozygous twin studies[5] and familial aggregation in several populations.[6–8] Despite recent advances in defining the molecular basis of T2D, the mode of inheritance of this disease is still debated. Several studies have shown that individuals with maternal history of diabetes are at a higher risk of developing the disease than individuals with a paternal diabetes history. The majority of these studies were performed on Europeans, Asians, Americans, and Africans (black South Africans).[7 9–12] To our knowledge, no studies on familial aggregation of T2D and transmission patterns of the disease in North Africans have been reported. Our aim is to estimate the degree of familial aggregation of T2D in the Tunisian population and to investigate transmission patterns of this disorder and their relationships with patients' clinical characteristics.

SUBJECTS AND METHODS

Subjects

Subjects with diabetes were recruited randomly at the National Institute of Nutrition (Tunis, Tunisia), a referral diabetes medical centre in Tunisia. A sample of 189 unrelated Tunisian patients with T2D was enrolled. T2D was diagnosed according to World Health Organization criteria. Clinical and biochemical parameters were determined (body mass index (BMI), systolic and diastolic blood pressure, cholesterol, triglycerides, glucose levels, HbA_{1C}). Type 1 diabetes was specifically excluded on the basis of loss of weight with low BMI and the presence of ketoacidosis or ketosis and continuous requirement for insulin in the first months of diagnosis. Patients were interviewed about their family history of diabetes. This study was approved by the institutional ethical committee. All participants gave their informed consent and responded to an interview following a detailed questionnaire (to avoid misinterpretation) regarding the diabetes status of their parents, siblings, uncles and aunts from both maternal and paternal sides. Data were reported in a genealogical tree. Relatives with diabetes were classified into two groups: first degree for parents and siblings, and second degree for uncles and aunts.

Statistical analysis

The maternal effect was first tested among parents (mother vs father) and then among aunts and uncles (maternal vs paternal side). Comparison of proportions was performed by χ^2 test (McNemar). To assess differences in the metabolic parameters between patients according to their parents' diabetes status, Student's t test was used for comparison of two means; a value of $p<0.05$ was considered significant.

RESULTS

Frequency of diabetes among patients' relatives

All cases with at least one uncertain or unknown relative diabetes status were excluded and complete datasets on family history of diabetes (mothers, fathers, sisters, brothers, aunts and uncles from both maternal and paternal sides) were

Abbreviations: BMI, body mass index, T2D, type 2 diabetes mellitus

obtained for 132 subjects (78 women and 54 men) with a mean (SD) age of 58.8 (9.4) years, a mean duration of diabetes of 15.1 (6.6) years and a mean BMI of 28.6 (5.6). These basic demographics are similar to those of the entire population being sampled (A Abid, unpublished data). From the family trees, information was gathered for a total of 1767 individuals. Diabetic relatives were classified into two groups: first degree for parents and siblings (n = 928) and second degree for uncles and aunts (n = 839).

The frequencies of diabetic relatives are given in fig 1. Among patients, 93 (70%) had at least one affected relative and 57 (43%) had at least two diabetic family members. When classifying these relatives according to first and second degree, 77 (58%) patients reported at least one parent or sibling with diabetes, 53 (40%) had at least one affected uncle or aunt from either maternal or paternal sides, and 37 (28%) had both first and second degree relatives with diabetes. Overall, of those patients with a history of diabetes in first degree relatives, 45 (34%) had at least one parent with diabetes, and 59 (45%) had at least one sister or brother with diabetes. Among the latter group, 25 (19%) had at least two siblings with diabetes, and 27 (20%) had at least one parent and sibling with diabetes. For diabetic subjects with a positive history of diabetes among second degree relatives, 24 (18%) had at least two affected family members among their aunts or uncles from the maternal or paternal side. Overall, 16% of first degree relatives are affected compared to 12% of second degree relatives ($p = 0.01$), thus suggesting familial aggregation of T2D (fig1).

Maternal effect

In order to estimate the parental transmission of T2D, patients were divided according to their parents' and uncles/aunts' status, respectively. Results showed that among the diabetic subjects, 45 (34%) had at least one parent with diabetes, 28 (21%) had only an affected mother (maternal), 13 (10%) had only a diabetic father (paternal), and 4 (3%) had both parents affected (bilineal) (fig 2A). Therefore, patients were more likely to have a mother with diabetes than a father with diabetes ($p = 0.03$). A positive history of T2D was more common among maternal aunts/uncles than in paternal aunts/uncles (29% vs 16%, respectively, $p = 0.01$), suggesting that this maternal effect likely extends to the previous generation in second degree relatives (fig 2B). In summary, 41% of subjects with diabetes have at least one affected relative on the maternal side compared to only 24% of patients with diabetes having at least one affected family member on the paternal side ($p<0.01$). Altogether, 10% of index patients had at least one affected family member on both sides.

Relationship between transmission patterns of T2D and patients' clinical characteristics

We finally examined the influence of various transmission patterns of T2D on clinical and metabolic factors. The probands were classified as maternal (if only the mother has diabetes), or paternal (if only the father has diabetes). Results showed no significant difference in clinical parameters between patients with paternal or maternal history of diabetes in the studied sample (table 1).

DISCUSSION

In Tunisia, as a result of changing lifestyles (types of food, sedentary behaviour) due to rapid urbanisation, the prevalence of T2D is increasing as is observed worldwide. However, the role of genetic and environmental factors remains unclear. Previous studies in Africans (black South Africans and Ethiopians),[7 13] Asians,[14] Europeans[15 16] and Americans[17] reported a significant positive family history of diabetes. To our knowledge, this is the first study to investigate the familial aggregation and transmission patterns of T2D in North Africans. To estimate the degree of familial aggregation of T2D in Tunisians, we observed that 70% of the subjects with diabetes in the present study had a positive family history of diabetes among at least one of their parents, siblings, uncles and aunts from both sides. These findings support familial aggregation of diabetes as reported in several populations with varying frequencies.[10 18] Thomas *et al*[19] observed that 66% of index patients from a French study had at

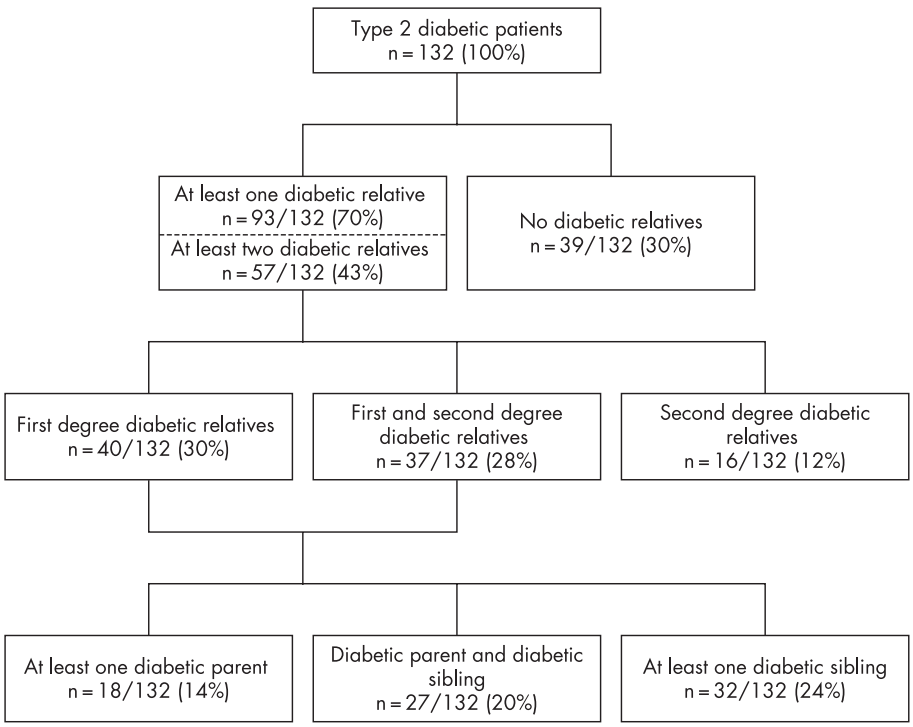

Figure 1 Family history of diabetes in the studied population. Flow chart showing the frequency of diabetes in relatives. Data are number (percentage in parentheses) of index patients having at least one first or second degree relative with diabetes.

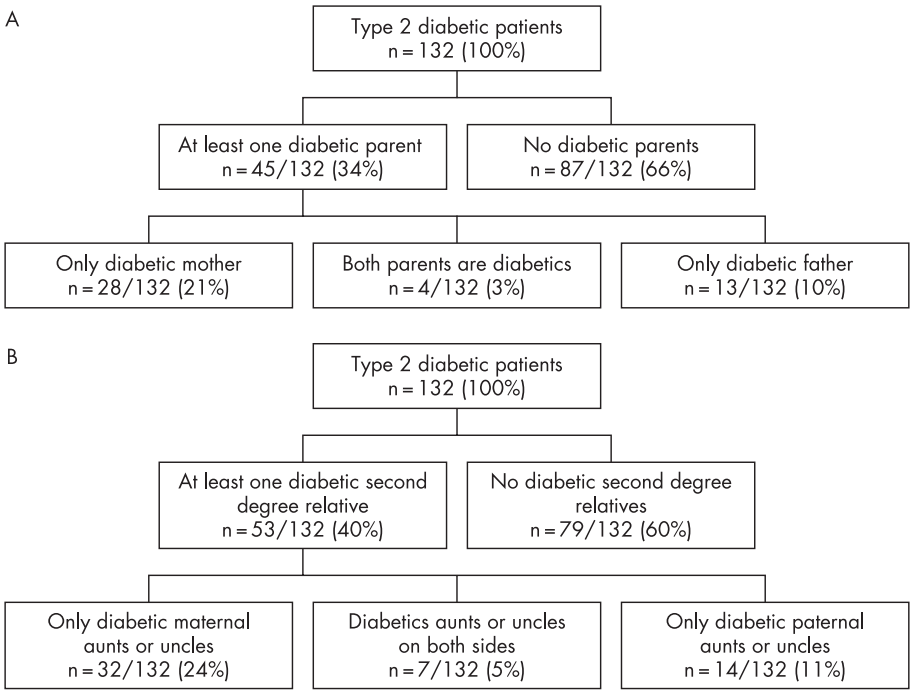

Figure 2 Assessment of the maternal effect. Flow chart showing the frequency of diabetes in relatives on maternal and paternal sides. Data are number (percentage in parentheses) of probands having (A) parents with diabetes and (B) second degree relatives with diabetes; p = 0.03 for mother vs father, p = 0.01 for maternal aunt/uncle vs paternal aunt/uncle.

least one relative with diabetes among their first and second degree relatives, while a study conducted in black South Africans[7] showed that only 27% of diabetic cases had a positive family history. Moreover, we noted that about 58% of diabetic probands had at least one affected first degree family member, a figure comparable to that reported by the CODIAB study (57%).[19] On the other hand, lower frequencies have been reported by other studies in Asians (36%)[8] and Europeans (33%).[16] Overall, 34% of diabetic subjects in the present study had at least one affected parent. Similar findings have been reported by other studies in patients with diabetes in the USA[17] and Sri Lanka,[10] whereas higher frequencies (53.9%) have been reported for South Indians.[20]

The genetic component of T2D in our population is supported by the frequency of diabetes in siblings of diabetic probands (45%). Investigation of parental transmission patterns of T2D showed an excess of maternal transmission of T2D as mothers were implicated two times more frequently than fathers, a figure which is also observed among second degree relatives. The maternal transmission of T2D is controversial. This inheritance pattern has been reported for several populations (English, French, black South African, Chinese and North American)[7 8 15 17 19] but ruled out in others (South Indians, Koreans and Mexican-Americans).[20–22] This discrepancy could be partly attributable to censoring and reporting biases as discussed by previous studies.[10 19] In addition more frequent diabetes screening among women because of pregnancy, the earlier onset of diabetes and the longer average lifespan could account for potential biases. In the Tunisian population, mean (SD) age at onset (47 (10) years for women and 49 (9) years for men) of diabetes and average life span (75 years for women vs 71 years for men) do not differ significantly between the two genders (H Ben Romdhane, National Health Survey, Tunisia). Hence, the hypothesis that fathers of diabetic subjects may be more likely to die of insulin resistance associated with cardiovascular disease before onset of T2D than mothers is unlikely.[22 23]

Table 1 Clinical and biochemical characteristics of patients according to their parents' diabetes status

	Parental diabetes	
Variables	**Maternal**	**Paternal**
n	28	13
Age at diagnosis (years)	40 (7.3)	37.6 (7.5)
BMI (kg/m^2)	28.58 (4.4)	26.92 (4.88)
SBP (mm Hg)	139.5 (15.9)	133.1 (11.8)
DBP (mm Hg)	81.1 (4.1)	79.6 (2.3)
Total cholesterol (mmol/l)	5.25 (0.72)	5.10 (1.04)
Triglyceride (mmol/l)	1.67 (0.65)	1.97 (0.82)
Fasting plasma glucose (mmol/l)	12.34 (3.13)	12.26 (2.66)
2 h plasma glucose (mmol/l)	15.35 (3.75)	15.96 (4.55)
HbA_{1C} (%)	9.23 (1.52)	9.18 (1.65)

BMI, body mass index; DBP, diastolic blood pressure; HbA_{1C}, glycated haemoglobin; SBP, systolic blood pressure.
Data are presented as mean (SD).
There is no significant difference in clinical and biochemical characteristics between patients with paternal or maternal history of diabetes.

Another hypothesis is that individuals may have more knowledge about their mothers' health status than they do about their fathers'. This should not be the case in our study because of cultural background. This is supported by the fact that for all the patients, the number of probands who had no knowledge of their mothers' or fathers' diabetes status were similar (10.05% vs 10.6%, respectively). On the other hand, a bias due to female preponderance is also unlikely as a study conducted by the Tunisian National Institute of Public Health reported that diabetes affects 8.4% of men and 8.7% of women (H Ben Romdhane, National Health Survey, Tunisia, 2005) and in the studied sample females do not have higher BMI (a risk factor for T2D) than males (29.1 (5.3) vs 27.9 (5.9), respectively, p = 0.2). Moreover, all cases reporting missing data or being uncertain about data for at least one parent were excluded. Nevertheless, influence of maternal genetic as well as environmental factors could not be ruled out.

Mutations in the mitochondrial genome[11] and genetic factors responsible for birth weight may contribute to the observed maternal effect.[24] Several studies reported that the intrauterine

environment may also be implicated in the maternal influence.[25 26] Interestingly, a study in Pima Indians showed that offspring of women who were diabetic during pregnancy were more likely to develop diabetes than the offspring of women who developed diabetes later.[27] Moreover, it has been shown that abnormal fetal nutrition is associated with the development of T2D later in adulthood.[28] Previous studies showed a positive association between maternal history of diabetes and lipid profiles.[8 29 30]

The influence of various transmission patterns of T2D on clinical and metabolic factors have been examined for 41 individuals for whom complete information was available. Results showed no significant difference in clinical parameters between patients with paternal or maternal history of diabetes in the studied sample. Studying a larger sample will probably provide a better view on this relationship.

In conclusion, our study gives insight on familial aggregation as well as maternal transmission of T2D in the Tunisian population studied. Segregation analysis of a larger sample and molecular investigation of candidate genes will help to evaluate better the aetiology of the maternal effect on this disease.

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